

## XXV-3. *The Bladder*

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### Urothelial Tumors

Transitional epithelium lines the urinary tract from the calyx through the proximal third of the urethra, and tumors arising from it often have the same histologic appearance and very likely arise from the same carcinogenic stimuli. They constitute about 98% of neoplasms occurring in the renal pelvis, ureter, and bladder.

### Bladder Carcinoma

Of all urologic neoplasms, these tumors pose the most serious problems of management. Knowledge of their existence extends to antiquity, but precision in diagnosis had to await the invention of the incandescent light by Thomas Edison in 1880. Max Nitze had produced the first cystoscope in 1876, but Edison's lamp actually lit the way to urology. The instrument allowed for the acquisition of data concerning not only the bladder, but also the state of both upper tracts in a fashion only hoped for just a few years earlier. The other great event that played an essential role in the development of urology was the invention of media for intravenous urography. The first material, called "Uroselectan," was a product of German scientists, who produced the first intravenous studies in 1929. One might view this as the beginning of modern knowledge about bladder carcinoma.

The term "bladder carcinoma" encompasses a group of neoplasms that are exceedingly heterogeneous. They are prone to recur, and recurrent tumors are likely to be more aggressive than their predecessors. The

American Cancer Society has estimated that 6300 men and 2900 women will die of bladder cancer in the United States in 1973, and that 20,800 new cases will be diagnosed.

**Etiology.** Although the cause of bladder carcinoma in nearly all patients is unknown, its occurrence in certain industrial workers has led to the identification of a group of dangerous compounds. In addition, it has directed investigators' attention to possible natural metabolites that, because of their similarity to those industrial compounds, may be responsible for the production of many instances of bladder carcinoma.

Bladder cancer is believed to occur in human beings after exposure to certain aromatic amines and is associated with bilharzial infestation in Egypt. It also occurs in domestic animals, notably cows in Turkey that eat bracken fern. It may be produced in many experimental animals with a variety of compounds.

Rehn, in 1895,<sup>44</sup> was the first to report on bladder cancers in man that may have been caused by a carcinogen. These carcinomas, termed "aniline cancers," were found in men who worked with dyestuffs, but it was not appreciated that the causative agent was probably an aromatic amine until nearly forty years later, when Ferguson et al. reported on 23 patients with bladder cancer who worked in an American plant that had started operation in 1917.<sup>20</sup> These workers were exposed to 2-naphthylamine. Subsequent experiments in dogs proved that feeding this compound produced bladder cancer,<sup>25</sup> that bladder cancer would not appear if the urine were diverted, but that renal pelvic and ureteral cancers would develop instead,<sup>45</sup> and that the metabolite,

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### Exhibit C

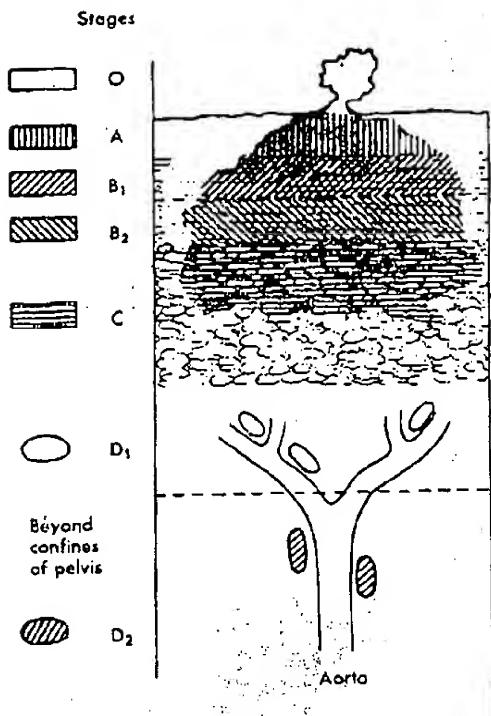


FIG. XXV-3-4. A system for clinical staging. (Adapted from Jewett and Strong,<sup>24</sup> and from Marshall.<sup>25</sup>)

sis demonstrated urographically; and (3) a mass palpable bimanually.

Tumors that are noninvasive rarely metastasize, whereas those that do invade the bladder wall metastasize with a frequency that is proportional to the depth of invasion. These tumors are often palpable, and experience has demonstrated that about half the patients with muscle invasion will have pelvic nodal metastases. The nodes involved first are those in the obturator space; second, the hypogastric and external iliac groups; and last, the common iliac and periaortic groups. There is also excellent clinical evidence to prove that even though pelvic nodes are not demonstrably involved, there is a strong likelihood that distant but silent pulmonary, liver, and/or bony metastases are present if muscle invasion has occurred.

The Jewett-Strong-Marshall staging system has been widely adopted and is used

by clinicians and pathologists alike. In the hands of urologists involved in a Cooperative Group Study,<sup>43</sup> the correlation between clinical and pathologic stages falls far short of Marshall's accuracy. Their clinical estimates and the pathologic stages are shown in Table XXV-3-1, where errors in the control group were so great (Stage B<sub>1</sub>, 46%; B<sub>2</sub>, 53%; and C, 30%) that the true effect of preoperative irradiation could not be determined. Clearly, the clinician must use his tools better, or new ones must be developed, because the therapeutic plan outlined for each patient depends on the estimate of stage. In this regard, new techniques for staging are in very short supply. Conventional lymphangiography is almost worthless, though the multiple contrast studies proposed by Lange deserve careful evaluation.<sup>31</sup> Conjecturally, one wonders if an ultrasound device in a catheter might not add precision.

**Clinical Manifestations.** Painless hematuria is the first symptom in about 75% of patients. It is usually total and sometimes clots are present. Clot retention is not frequent, though it may occur when tumors are large and ulcerated.

Painful hematuria occurs with infection, and suprapubic pain after voiding may occur when the lesion is invasive. Normally, the bladder urothelium slides over the underlying detrusor in a fashion that provides for relatively rapid changes in volume, but when tumor fixes the urothelium to the underlying muscle, distensibility is reduced and motion in the form of emptying is painful, sometimes exceedingly so.

Patients report frequency and nocturia, as well, but these too are usually later symptoms. Occasionally the tumor may be silent until it obstructs a ureteral orifice. Hydrocephrosis and subsequently pyelonephritis may be the first symptoms, but this is rare. If the patient has neglected to seek advice and treatment, he may also complain of weight loss.

Neglect of the patient with hematuria by mistreatment with pills is a commonly encountered occurrence. Next to total prevention, early diagnosis will yield the highest